Pharmacokinetics of Estrogen

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The main types of pharmacologic therapy used to treat the hormone deficiency of menopause are parenteral and oral administrations of estrogen. Parenteral administration results in predictable absorption without major intermediary metabolism, whereas all oral estrogens are subject to intestinal metabolism before entering the systemic circulation. Various options are available. Injectable estrogens, because of rapid absorption and metabolism, are impractical for long-term replacement therapy. The primary drawback to subcutaneous estradiol pellets is the surgical procedure required for their insertion and removal. Vaginal epithelium is an effective pathway for absorption of estrogen given by solution, tablet, or cream, although only the latter is currently approved for clinical use; relatively constant serum levels of estradiol can be obtained with vaginal rings. Transdermal patches provide controlled hormone levels for up to 3.5 days. Although oral conjugated equine estrogens have been used extensively, they introduce types of estrogen, such as equilin, that are not naturally found in humans and that can produce a pronounced hepatic response. Micronized estradiol, oral estrone, and other estrogens have been used as alternatives to equine estrogens. Clinicians should understand the pharmacokinetics of the various options for replacement therapy and select a course of treatment that is safe, effective, and convenient for the patient. (*Obstet Gynecol 75:9S, 1990*)

In comparing the specifics of various types of estrogen administration for treatment of the menopause, it may be helpful to consider the concept of menopause as an endocrinopathy. An endocrinopathy is a disorder in the function of an endocrine gland and the consequences of that dysfunction.[1] In the case of menopause, a specific endocrine gland has failed, namely, the ovary. Specific endocrine products are subsequently deficient, primarily estradiol-17β and progesterone.[2] Specific pathologic conditions develop because of the endocrine deficiency, eg, postmenopausal osteoporosis, urogenital atrophy, and vasomotor instability. Finally, treating the endocrine deficiency with hormone replacement can prevent, delay, or ameliorate many of the pathologic consequences of the endocrine deficiency.[3,4] Properly designed endocrine replacement would, in general, meet the following criteria: to replace the specific hormone that is deficient, if possible; to replace the hormone using a dose, pattern, and portal of entry that at least approximate the characteristics of the functioning gland; and to relieve or prevent as many as possible of the pathologic consequences of the endocrine deficiency, while at the same time avoiding the unphysiologic consequences of exogenous hormone administration. With these concepts in mind, we can examine menopause—irreversible ovarian failure—as an endocrinopathy and analyze the pharmacologic options that we have available for replacement therapy.

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Defining the Hormone Deficiency

The principal estrogen produced by the functioning premenopausal ovary is estradiol-17β, produced primarily in the ovulatory follicle during each cycle.[3,5] During normal ovulatory cycles, ovarian production of estradiol-17β ranges from 60–600 μg/day, resulting in circulating levels of estradiol-17β in serum ranging from 40–400 pg/mL.[6] As a woman ages, ovulation becomes less frequent and less predictable, resulting in diminished production of estradiol-17β.[2] At the point of irreversible ovarian failure at menopause, no further ovulatory follicles are produced, and production of estradiol-17β decreases dramatically.[7] After menopause, the ovarian production rate of estradiol-17β is less than 20 μg/day and circulating levels of estradiol-17β in serum are less than 30 pg/mL.

The second major naturally occurring human estrogen is estrone.[2] Estrone is derived principally from two sources: from metabolism of estradiol-17β and from aromatization of androstenedione in adipose tissue.[2] Therefore, before menopause, as a result of the fluctuating levels of estradiol-17β during the ovulatory cycle, circulating levels of estrone may also fluctuate, ranging from approximately 40–200 pg/mL. Through most of

the cycle, the estradiol-to-estrone ratio is generally greater than 1.0.[6] The other source of estrones, androstenedione, is produced mainly by the adrenal gland and to a lesser extent by the functioning ovary.[5] After menopause, androstenedione remains largely unchanged because the adrenal gland continues to function normally.[7] Some researchers have reported a significant decrease in androstenedione levels after the menopause, although net levels of estrone remain constant because peripheral conversion increases. Furthermore, the amount of adipose tissue is unchanged, and may in fact increase with aging, so the aromatization of androstenedione to estrone continues or may increase.[8] After menopause, estrone levels in serum remain above 40 pg/mL, and the estradiol-to-estrone ratio is reversed, to less than 1.0.[6] Thus, there is no significant deficiency of estrone after menopause.

Both estradiol-17β and estrone are subject to metabolic conversion to less active compounds and to conjugation in preparation for their excretion.[8] In humans, all estrogens, conjugated or unconjugated, are found in the circulation either physiologically free (ie, either unbound or weakly associated to serum albumin by nonspecific binding) or specifically bound with high affinity to sex hormone-binding globulin.[9] Serum binding affects the ability of estrogen to enter the cell. Estrogens exert their activity by interaction with intracellular receptors. The relative activity or "potency" of a specific estrogen depends upon its availability to cross the cell membrane, bind to a specific receptor, activate the receptor effectively, and release the receptor for further binding. Because of this, the most active naturally occurring human estrogen is physiologically free estradiol-17β, with physiologically free estrone being somewhat less active. Estradiol and estrone that are specifically bound to sex hormone-binding globulin are not thought to be available to cross the cell membrane and therefore are considered biologically inactive. Estrogen metabolites, such as estriol, epiestriol, and catechol estrogens, have little estrogen activity primarily because of relatively low affinity for the estrogen receptor. Estrogen conjugates, such as estradiol glucuronide, estradiol sulfate, estrone glucuronide, and estrone sulfate, are highly water-soluble and thus do not readily cross the cell membrane. However, these conjugates may be converted back to biologically active estradiol or estrone by cleavage of the sulfate or glucuronide group from the molecule.[8]

It is interesting to note the extent to which the liver influences estrogen metabolism and is, in turn, influenced by estrogen status. The liver is the principal site for the conjugation of estrogen in preparation for subsequent excretion by the kidney. The liver also excretes estrogens itself directly by means of bile excretion. The liver is a principal organ involved with the absorption of estrogens from the gastrointestinal tract and with reabsorption of estrogen that has been excreted in the bile. The liver produces sex hormone-binding globulin, which determines, in part, the specific binding and therefore the bioavailability of estrogens and other sex steroids in the circulation.[8] Several metabolic functions of the liver, such as protein production (including binding proteins and clotting factors), carbohydrate metabolism, lipid metabolism, and bile production, are influenced by exposure to estrogen and other sex steroids.[9,10] It is clear that the liver is intimately involved with the metabolism of the sex steroids, in a complex and sensitive interaction.

The above factors are important in examining the effects and metabolic fate of exogenous hormones administered for replacement therapy.

Forms of Replacement

From the foregoing discussion, it seems likely that any estrogen capable of binding to the estrogen receptor, that is administered in sufficient quantity and delivered by any practical route of administration, will be able to prevent, delay, or ameliorate the pathologic consequences of estrogen deficiency. In actuality, however, the tolerability, side effects, and pharmacologic consequences of a particular type of estrogen administration may make that method impractical.

The major useful forms of estrogen therapy are parenteral administration and oral administration. Specific types of parenteral administration include injection, subcutaneous pellets, transvaginal administration (by cream, solution, tablets, or silastic rings), percutaneous administration (by gel), and transdermal administration (by patch). Several different estrogens may be administered effectively by the parenteral route, although estradiol-17β is probably most commonly selected. The various parenteral administrations are generally characterized by predictable absorption without major intermediary metabolism. At present, oral administration of estrogen is accomplished only by tablet form, which may contain any one of several different types of estrogen including conjugated equine estrogens, estradiol, or estrone. All forms of oral estrogen are subject to intestinal absorption and metabolism before entry into the systemic circulation.[11]

We will consider examples from each of the major types of estrogen administration with attention to absorption, metabolism, and pharmacologic peculiarities of administration.

Parenteral Administration

Injection

As early as 1912, aqueous or lipid extracts of ovarian tissue were shown to have estrus-producing properties when injected. However, because estrogens in general are very poorly soluble in water, aqueous suspensions are largely impractical for long-term replacement therapy. Estrogen preparations in oil are generally rapidly absorbed after injection and are quickly metabolized. Estradiol esters are less polar, so their rate of absorption from oil injections is slowed and the therapeutic effect is prolonged.[11] For example, estradiol valerate and estradiol cypionate, in concentrations ranging from 1–40 mg/mL, are active for several weeks after a single intramuscular injection. Polyestradiol phosphate, approved for treatment of prostatic cancer but not for postmenopausal replacement therapy, releases estradiol from the parent molecule after intramuscular injection. Estrone and "natural estrogenic substance" (estrone) are also available in solution for injection.[12]

Subcutaneous Pellets

Pellets containing pure crystalline estradiol-17β have been studied and used clinically.[13–15] Pellets of 25 mg estradiol produce serum levels of estradiol of approximately 50–70 pg/mL, and those of 50 mg estradiol give levels around 100–120 pg/mL for up to several months. There appears to be little metabolism of estradiol in the subcutaneous tissue, so there is a preferential increase in estradiol rather than in estrone or other metabolites. The levels appear to be relatively constant in the serum, and patients report good relief of symptoms.[13] For patients who have difficulty remembering to take medication, the single insertion of a pellet every several months may have advantages in terms of compliance. Nevertheless, using subcutaneous pellets has several disadvantages as well. A minor surgical procedure is required to insert them. Infection at the site of insertion is possible. They are difficult or impossible to remove should a problem develop, and any attempted removal also requires a minor surgical exploration of the site. Chiefly because of the concerns about the difficulty of stopping therapy if necessary, estradiol pellets have relatively little popularity today.

Vaginal Creams

In the past, vaginal creams containing estrogen were suggested as a mechanism for relieving urogenital symptoms in women who were not candidates for systemic estrogen. By 1978, however, it was recognized that estrogen is readily absorbed through the vaginal epithelium when estrogen creams are administered, so vaginal estrogen creams are, in fact, a means of parenteral administration.[16] Unfortunately, many patients find creams messy to use, and it is difficult to control dosage. For these reasons, systemic administration of estrogen by means of vaginal creams is not widely used clinically. Creams containing conjugated equine estrogens, estropipate, or dienestrol are currently marketed in the United States for vaginal administration.[12]

Vaginal Solutions and Tablets

Because most estrogens are lipophilic, they are absorbed readily across any epithelium, including vaginal epithelium. A solution of 0.5 mg estradiol placed in the vagina is absorbed rapidly, with little change in estrone, suggesting that there is little metabolism of estradiol as it passes through the vaginal epithelium. After absorption, the serum levels of estradiol return to baseline within about 6 hours after application. Similarly, a solution containing 0.5 mg estrone produces a rapid increase in serum levels of estrone, with little change in estradiol, and a return to baseline within about 6 hours after administration.[17] In an attempt to prolong the absorption curve, tablets of estradiol have also been tested for vaginal administration. Once again, the vaginal epithelium is capable of absorbing the estrogen with little intermediate metabolism. The estradiol levels in serum reach approximately 1000 pg/mL, considerably above the highest levels seen in the spontaneous menstrual cycle, but return to baseline by 24 hours. There are no estrogen solutions or tablets approved for clinical use in the vagina at present.

Vaginal Rings

In view of the rapid absorption of estrogen through the vaginal epithelium and the problems of bolus absorption outlined above, attempts have been made to design a sustained-release system for long-term delivery of estradiol from the vagina. One biologically inert polymer, polydimethylsiloxane, is capable of releasing estrogen from its matrix in a predictable fashion. To prepare the delivery system, pure crystalline estradiol-17β is mixed with the liquid polymer, polymerization is initiated by addition of an appropriate catalyst, and the liquid is injected into a mold of appropriate design. The finished rings are toroidal in shape and range up to 55 mm in diameter.

The absorption of estradiol from the vaginal epithelium depends, in part, on the surface area of the ring

selected[18] (also Stumpf PG, Maruca J, Santen RJ, Demers LM. Physiologic estradiol replacement by intravaginal ring. Clin Res 1981;29A:666). Vaginal rings containing 100, 200, and 400 mg estradiol-17β have been tested. The 100-mg estradiol vaginal ring produces levels of estradiol in serum of approximately 40–50 pg/mL, the 200-mg ring produces levels around 70–80 pg/mL, and the 400-mg ring produces levels around 140 pg/mL. These levels can be maintained in a fairly constant fashion for up to 3 months using a single ring.[19] The rings may be removed periodically for a short time for cleaning and patient hygiene. There appears to be preferential absorption of estradiol, with little intermediate metabolism through the vaginal epithelium. The comfort and compliance of study subjects have been good. The levels of hormone achieved can be modulated rather precisely[20–24] (also Veldhuis JD, Evans WS, Rogol AD, Kolp LA, Thorner MO, Stumpf PG. Dual mechanisms subserve the positive feedback actions of estradiol on gonadotropin secretion in man. Clin Res 1986;34A:647). The estradiol levels in serum rise rapidly when the system is put in place and fall rapidly when the system is removed. It is possible to administer several different rings to mimic the steroid levels of the menstrual cycle. It is also interesting that progesterone may be administered in a similar fashion, should that be desirable.[25–27] This has led to some investigational uses of progestogen administration by vaginal ring, but none have been approved for clinical use.

Percutaneous Estradiol Cream or Gel

A gel preparation containing estradiol has been studied in Europe. Application of this material to the skin, usually the anterior abdominal wall, results in absorption of the estrogen compound, elevation of circulating serum levels of estrogen, and clinical relief of symptoms.[28–30] However, as is the case with vaginal estrogen creams, the percutaneous cream or gel may be messy and precise control of dosage may be difficult.

Transdermal Estradiol

As a further refinement of administration methods that take advantage of epithelial absorption of estrogen, a transdermal patch has been designed, tested, and approved for clinical use. In the United States, patches delivering 0.05 or 0.1 mg/day of estradiol are available. The patch consists of several layers: 1) an occlusive membrane that prevents evaporation, 2) a reservoir containing estradiol-17β dissolved in an alcohol solution, 3) a microporous membrane controlling the release of the estradiol, 4) an adhesive layer that attaches the patch to the skin, and 5) a disposable protective film that covers the adhesive before application. The patches are individually sealed in foil envelopes and are packaged to contain 1 month's supply per box. One patch is applied to the skin, usually on the lower trunk, and changed twice per week, that is, every 3.5 days. Absorption of estradiol through the skin occurs rapidly when the first patch is applied. There appears to be little intermediate metabolism through the epidermis. The serum levels of estradiol remain fairly constant for up to 84 hours, after which the absorption decreases quickly. When the last patch is removed, serum levels of estradiol fall rapidly, and excretion of estradiol in the urine is at baseline levels by 24–48 hours after removal. Consistent with the rise in estradiol levels, the following have been observed: relief of hot flashes and other menopausal symptoms, suppression of gonadotropins, reduction in urinary excretion of calcium, and maintenance of bone density.[31–38] This system offers the advantages of parenteral, convenient administration and precise control of dosage.

Oral Administration

Conjugated Equine Estrogens

Estrogens were identified in the urine of animals over 60 years ago. Estrogen purified from the urine of pregnant mares became one of the earliest hormones for replacement therapy. As described above, endogenous estrogens are metabolized and conjugated by the liver in order to increase their solubility in water in preparation for excretion. For this reason, the estrogens obtained from urine represent a mixture of estrogen compounds, most of which are estrogen sulfates or glucuronides. Furthermore, the urine of horses specifically contains certain estrogens, such as equilin, that are characterized by additional double bonds in the B ring of the molecule and that are not normally found in humans at all. Nevertheless, this mixture of conjugated equine estrogens has a long history of clinical usefulness.

The pharmacokinetics of orally administered conjugated equine estrogens are complicated because so many different types of estrogenic compounds are administered, which are in addition subject to metabolic conversions in the gastrointestinal tract. The separation and identification of these compounds from blood samples are tedious, and the assays for some of them, such as equilin, are not readily available. Oral conjugated equine estrogens at doses that are clinically useful, such as 0.625 or 1.25 mg/day, produce levels of estradiol and estrone similar to those seen in the normal menstrual cycle. The levels of equilin that

result from these doses of oral estrogens are many times higher than the levels of estradiol or estrone achieved. These same doses of oral conjugated equine estrogens are associated with increases in certain liver proteins, such as renin substrate, that are higher than levels seen in normal premenopausal women. These exaggerated pharmacologic responses by the liver are not necessarily clinically significant. For example, although renin substrate increases, there is no clinical increase in blood pressure associated with oral administration of conjugated equine estrogens in postmenopausal women. There has been clinical concern that these pharmacologic effects on the liver may eliminate some potential candidates for estrogen replacement. On the other hand, certain liver responses, such as changes in high-density lipoprotein cholesterol, are believed to be beneficial. It is not clear at this time how much the specific liver effects are associated with the characteristics of oral administration per se rather than with the increase in estrogen levels in the circulation.

Oral Estradiol

In the past, oral estradiol tablets were absorbed poorly and the estradiol was rapidly metabolized and inactivated. The use of micronized estradiol preparations has resulted in more reliable absorption and is clinically effective. Even micronized estradiol is subject to gastrointestinal metabolism, however, with significant conversion to estrone and other estrogens before entry into the general circulation. To date, there is much less specific information available regarding oral estradiol as compared with oral conjugated equine estrogens.

Oral Estrone

Oral administration of estrone has been proposed as a "safer" form of estrogen replacement therapy because it was believed to induce less proliferative stimulation of the endometrium. However, because it appears that all estrogens exert their effects through a common intracellular receptor, it seems unlikely that estrone, at clinically useful doses, would somehow spare the endometrium. Estrone, at appropriate doses, provides clinical relief of symptoms, but there is little objective evidence that the use of oral estrone is inherently safer.

Other Oral Estrogens

Ethinyl estradiol is the most commonly used estrogen in combination oral contraceptives. In part because of its pronounced effect on liver proteins, it is not currently used for postmenopausal estrogen therapy. Diethylstilbestrol is a potent nonsteroidal estrogenic compound, but it also has no present role in postmenopausal estrogen replacement, although it is still available for use in palliative treatment of prostate cancer. Quinestrol is a steroidal estrogen that appears to be stored in adipose tissue after oral administration, then gradually released back into circulation. In clinical practice, a loading dose of daily administration is given for 1 week, after which once-weekly tablets are taken. Because it may be difficult or impossible to stop therapy quickly if desired, this particular estrogen has gained little popularity.

Summary

Menopause is an endocrinopathy. The specific hormone deficiency and its effects may provide a framework for the critical analysis of possible options for replacement therapy. Parenteral administration allows delivery of the specific hormone that is deficient, namely estradiol-17β, permitting clinically effective replacement therapy with minimal pharmacologic impact. Oral administration of estrogen has been well studied, and in general appears to be clinically safe and effective, despite theoretical disadvantages associated with the oral route. Therefore, selection of a particular form of estrogen replacement therapy may be made on an individual basis with considerations of safety, effectiveness, and convenience for the patient.

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